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Quantitative fetal fibronectin predicts preterm birth in women with bulging fetal membranes

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OBJECTIVE: To assess the predictive value of quantitative fetal fibronectin (fFN) concentration in cervicovaginal fluid for spontaneous preterm birth in women with bulging fetal membranes.

STUDY DESIGN: This was a prospective observational study from five UK tertiary centres of a cohort of women with singleton pregnancy and bulging fetal membranes presenting between 18 and 32 weeks of gestation (n=62), in the period 2010-2014. fFN concentrations in cervicovaginal fluid were measured both quantitatively and qualitatively at presentation in all women. Predictive statistics and receiver operating characteristic (ROC) curves were calculated for both tests to predict spontaneous preterm birth within 14 days from testing and before 34 weeks of gestation.

RESULTS: 62 eligible women with bulging fetal membranes were recruited from screening of 2571 women at high risk of preterm birth. The median gestational age was 24^{+0} (LQ-UQ, 21^{+2}-25^{+3}) at presentation and 34^{+4} (25^{+2}-39^{+0}) at delivery, with a median time from testing to delivery of 58 days (17-110). Concentration of quantitative fFN at presentation correlated negatively with time to delivery (Spearman's r_s=-0.615, p<0.001). The area under the ROC curve for quantitative fFN testing was 0.81 (95% CI 0.69-0.94) for prediction of spontaneous preterm birth within 14 days, and 0.84 (0.73-0.95) before 34 weeks of gestation.

CONCLUSION: Quantitative fFN has a role in predicting spontaneous preterm birth even in women with bulging fetal membranes, suggesting that fFN leakage could potentially be an active process. This may aid the clinical management of this high-risk group in the future.

Key words: bulging fetal membranes; fetal fibronectin; preterm labor; sensitivity and specificity

Condensation: Quantitative fetal fibronectin can help predict spontaneous preterm birth even in the presence of bulging fetal membranes.

INTRODUCTION

Preterm birth is the leading cause of neonatal mortality globally, directly responsible for over 15% of all neonatal deaths as well as short and long-term morbidity and disability [1,2]. Interventions such as timely antenatal steroid administration and in-utero transfer to specialist units have been shown to improve neonatal mortality and morbidity [3,4]. In women with bulging fetal membranes (BFM) at early gestations – a particularly high-risk group – the use of rescue cervical cerclage can delay delivery by approximately 5 weeks [5–7]. However, this frequently fails and could increase the risk of infection to mother and fetus; furthermore, some women presenting with BFM do not deliver prematurely even without intervention [8].

A bedside test for the analysis of fetal fibronectin (fFN) concentration in cervicovaginal fluid (CVF) (Hologic Rapid fFN TLi_{IQ}) can help predict spontaneous preterm birth (sPTB) in symptomatic and high-risk asymptomatic women before cervical dilation occurs, using a fixed threshold of 50 ng/ml to define a positive and negative result (qualitative test) [9]. fFN is a glycoprotein thought to contribute to the adhesion between chorionic and decidual tissue in pregnancy. Prior to preterm birth, disturbance of the integrity of the maternal-fetal interface, particularly the partial separation of the decidua from the fetal membranes, is believed to result in release of fFN into the CVF fluid. More recently, enhanced prediction has been demonstrated using a quantitative bedside test (qfFN, Hologic 10Q system) which provides additional incremental thresholds to define variable risk [10,11].

It is not known however whether CVF qfFN concentrations are uniformly raised after cervical dilation and membranes exposure has occurred, or whether the test may still be predictive of outcome in these circumstances and according to concentration. In view of the

high risk of sPTB in this group [6] and qfFN testing being now available at the bedside, an accurate prediction of clinical outcome would be useful and could help direct emergency obstetric management. The purpose of this study was to assess the predictive value of CVF qfFN in women with BFM to predict sPTB within 14 days of presentation and before 34 weeks of gestation.

MATERIALS AND METHODS

This was a predefined secondary analysis of a larger prospective cohort study (EQUIPP; Evaluation of Quantitative fetal fibronectin in Prediction of Preterm birth) of CVF qfFN concentration in women at high risk of sPTB, conducted between October 2010 and August 2014 at five UK tertiary referral centres.

Ethical approval was granted by the South East London Research Ethics Committee, and all local research ethics committees that were associated with participating centres. Women were recruited to the study if they had singleton pregnancies, and were considered high-risk for preterm birth (one or more of: previous sPTB <37 weeks' gestation; previous second-trimester miscarriage ≥16 weeks; previous invasive cervical surgery; uterine abnormality; incidental finding of a short cervix <25 mm or symptoms suggestive of preterm labour or bulging membranes e.g. abdominal pain, vaginal pressure, increased discharge). Women were enrolled in this sub-analysis at the time they had BFM noted at speculum (any degree of cervical dilatation), if they were between 18 and 32 weeks of gestation, were not contracting, and underwent both quantitative (Hologic Rapid fFN 10Q) and qualitative (single-threshold Hologic Rapid fFN TLi_{IQ}) fFN concentration measurements. fFN testing was

performed prior to ultrasound scan or digital examination using previously described methods, in line with the manufacturer's guidelines [10]. Briefly, during speculum examination, a swab was inserted into the posterior fornix and rotated for 10 seconds until saturated, avoiding the cervix and fetal membranes. A single aliquot (200 µl) of the sample was analysed with the conventional qualitative analyser, and another with the quantitative one. The two tests were run concurrently and clinicians were made aware of the qualitative result, whereas the quantitative one was blinded (by generation of a 3 letter code). Women with blood stained CVF samples, sexual intercourse in the previous 24 hours, or suspected/confirmed rupture of membranes were excluded from the analysis, due to known interference with fFN measurement. Women with iatrogenic delivery prior to the outcome gestation of interest were excluded. Because of the technical difficulty and variability in recording cervical dilation with bulging fetal membranes, this was not included as a further parameter in our analysis.

The primary outcome for analysis was sPTB within 14 days from testing, with additional outcomes of sPTB prior to 34 weeks of gestation and time from testing to delivery. Statistical analysis was performed with SPSS v22 (Statistical Package for the Social Science, IBM). Previously established thresholds of qfFN (10, 50, 200, 500 ng/ml) [10,11] were used to determine sensitivity, specificity, positive and negative predictive values, likelihood ratios and relative risk for sPTB within 14 days and <34 weeks of gestation. Receiver operating characteristic (ROC) curves were calculated for both qualitative and quantitative fFN measurements. Further subgroup analysis was conducted based on gestational age at presentation: early (18-22 weeks), intermediate (23-27 weeks) and advanced (28-32 weeks). Variables are presented as median (lower quartile-upper quartile), mean ± standard

deviation, or frequency (percentage) where appropriate. This study is reported according to the Standards for the Reporting of Diagnostic accuracy studies (STARD) guidelines.

RESULTS

66 women fulfilling the inclusion criteria presented with BFM noted at speculum, of the 2571 high-risk women screened. Three were excluded due to blood staining of the CVF sample and one due to regular painful contractions at presentation (Figure 1). None had recent sexual intercourse and membranes were all visualised intact; there were no iatrogenic deliveries prior to 34 weeks of gestation. The demographic and clinical characteristics of the 62 women eligible for analysis are described in Table 1. Median gestational age was 24^{+0} weeks (LQ-UQ, 21^{+2}-25^{+3}) at presentation and 34^{+4} weeks (25^{+2}-39^{+0}) at delivery. 9/62 women (15%) presented with symptoms of bulging membranes (e.g. abdominal pain, vaginal pressure, increased discharge); the rest (85%) were incidentally discovered on speculum examination at routine clinical surveillance appointment. 29 (47%) women presented with a vaginal cerclage already in situ (history or ultrasound indicated cerclage earlier in the pregnancy), while 14 (23%) underwent rescue cerclage soon after presentation (all of whom were <24 weeks' at presentation). 13 women (21%) delivered spontaneously within 14 days of presentation, and 30 (48%) did so before 34 weeks of gestation.

Levels of fFN in CVF were measured in all 62 women, both with the quantitative system and with the qualitative test. Table 2 describes the distribution of women in each qfFN category and the rates of sPTB in each group. Two thirds of women with fFN ≥500 ng/ml had sPTB

within 14 days of testing, compared to 7% of those with fFN 10-49 ng/ml. No women with qfFN concentration <10 ng/ml delivered within 14 days.

The median time to delivery from fFN measurement was 58 days (17-110). When those who had a rescue cerclage at presentation were excluded, median time to delivery was 44 days (14-116). Spearman's rank-order correlation was significant between fFN concentration at presentation and number of days to delivery (r_s=-0.615, p<0.001), which appeared to follow a logarithmic trend (Figure 2). Mann-Whitney *U* analysis demonstrated a significant difference in the distribution of qfFN concentrations in women who delivered preterm compared to those who did not, both within 14 days from testing (p=0.001) and <34 weeks (p<0.001). Figure 3 shows the ROC curves for prediction of sPTB using qfFN, as well as the traditional qualitative test.

For prediction of sPTB within 14 days from testing, the area under the ROC curve (AUROC) for qfFN was 0.81 (95% CI 0.69-0.94), while that of the qualitative system was 0.68 (95% CI 0.53-0.83). For prediction of sPTB <34 weeks of gestation, the AUROC for qfFN was 0.84 (95% CI 0.73-0.95), and 0.76 for the qualitative test (95% CI 0.64-0.88).

Predictive statistics for sPTB within 14 days and prior to 34 weeks of gestation using qfFN are described in Tables 3 and 4 respectively. For delivery within 14 days, fFN≥10ng/ml had 100% sensitivity, while fFN≥500 ng/ml had 94% specificity.

These parameters did not differ significantly across subgroups of early (18-22 weeks), intermediate (23-27 weeks) and advanced (28-32 weeks) gestational age at presentation. The AUROCs for qfFN were respectively 0.83, 0.79, 0.75 for sPTB within 14 days, and 0.88, 0.82, 0.56 for sPTB <34 weeks.

When women who received rescue cerclage after presentation were excluded, ROC curves for prediction of sPTB <14 days and before 34 weeks of gestation subtended areas of 0.85 (95% CI 0.72-0.97) and 0.81 (95% CI 0.68-0.95) respectively. Further subgroup analysis was not conducted due to small numbers.

COMMENT

This study demonstrates the prognostic value of the qfFN assay to predict sPTB – both within 14 days of testing and before 34 weeks of gestation – in women with bulging membranes at extremely high risk of preterm birth. Our results show that the risk of preterm birth correlates with qfFN concentration in CVF even in women with BFM, a group traditionally thought to be at universally high risk of preterm birth. This might suggest that leakage of fFN into the CVF could be an active secretory process, related to risk of delivery following disruption of the maternal-fetal interface, rather than a passive mechanism initiated solely as a result of proximity of exposed fetal membranes to the vagina.

Women with BFM but very low concentrations of CVF qfFN have a low risk of subsequent delivery within 14 days of presentation compared with women with higher concentrations of qfFN (RR=9.3, 95% CI 1.3-65.2). In this cohort with BFM, no women with qfFN <10 ng/ml delivered within 14 days, while a quarter of those with qfFN concentrations ≥200 ng/ml and two thirds of women with qfFN ≥500 ng/ml delivered within this time frame. AUROCs for prediction of sPTB within 14 days from testing (0.81) and <34 weeks' gestation (0.84) demonstrate strong discriminatory power even in the presence of BFM. Furthermore, the positive prediction of qfFN at thresholds of 200 ng/ml was superior to the traditionally used

qualitative test (threshold of 50 ng/ml), whilst maintaining good negative prediction. Our subgroup analysis showed that these results remained consistent across early, intermediate and advanced gestational age groups. This is particularly reassuring in those who presented between 18 and 22 weeks' gestation, a high-risk group in which early intervention would be strongly considered. Sub-analysis was limited by our small study population, particularly for women of advanced gestational age at presentation (n=9), which could explain the decrease in the AUROCs for qfFN in this group.

Data collected prospectively onto a dedicated trial database ensured accuracy, and clinicians were blinded to the quantitative fFN concentration, so that management decisions were not influenced by the result. In spite of this unique group of very high-risk women, BFM is a rare event, limiting the ability to perform highly powered predictive statistics. Furthermore, 23% of our cohort received a rescue cervical cerclage, which might have delayed delivery and resulted in fewer events overall than expected. This would have reduced the calculated PPV, which could therefore be even higher than 67% without cerclage in situ. The ROC areas in the group without emergency cerclage are indeed reassuring. Of note, it was not standard practice in the United Kingdom to routinely prescribe progesterone to high-risk women, nor women with BFM.

To our knowledge, there have been no other studies evaluating the relationship between CVF qfFN concentration and subsequent preterm birth in this extremely high-risk group of women with BFM. Our group has previously demonstrated the predictive value of quantitative fFN measurement in women presenting with symptoms of preterm labour, with added risk discrimination over and above the traditional qualitative test [10], as well as

in asymptomatic women at high risk of preterm birth [11]. However, women with bulging fetal membranes were excluded from those analyses.

In this study, prediction of sPTB using qfFN compares favourably to high-risk cohorts described in the literature. For example, <2% (3/170) of those with qfFN concentrations <10 ng/ml delivered within 14 days in a group of women with a closed cervix (<2cm dilated) and symptomatic for threatened preterm labour [10], similar to our BFM cohort (0/11). In symptomatic women with fFN concentration ≥500 ng/ml and a closed cervix, risk of sPTB within 14 days was 46% (6/13) [10], compared to 67% (6/9) of women in our cohort with BFM.

The high risk of preterm delivery in our study population is reflected in the distribution of fFN concentrations detected. We found a uniquely high proportion of women with qfFN concentration ≥500 ng/ml (15%), compared with other studies of qfFN where concentrations ≥500 ng/ml (1-5%) [10,11] or even ≥300 ng/ml (10%) [12] are usually rare. Conversely, only 18% of women in our cohort had very low (<10 ng/ml) qfFN concentrations, compared to 57% reported in symptomatic women without BFM [10].

We confirm the clinical role of this bedside assay for the prediction of sPTB even in the context of BFM, suggesting that an active process could underlie fFN release. Whilst further larger studies are needed to validate these findings and evaluate their use in clinical practice, qfFN concentrations could potentially guide decisions such as in-utero transfer to specialist neonatal units, magnesium sulphate for neuroprotection, and steroid administration. The use of multiple thresholds could allow clinicians to alter decision-making based on a risk-benefit ratio for different interventions. For example, given that the beneficial effects of antenatal corticosteroids, routinely given to women with BFM, are lost

after 7 days [3] and repeated courses after this timeframe have been shown to reduce morbidity in preterm infants but with adverse effects on fetal growth [13], accurate timing is essential. qfFN could be a useful guide to target the group at highest risk, and avoid premature dosing. Given the high failure rate of rescue cerclage and the potential for morbidity associated with surgery and foreign materials, qfFN could be used to assist in the decision to insert cerclage. In women who present with bulging fetal membranes, qfFN can help to risk discriminate those likely to deliver soon.

CONTRIBUTIONS TO AUTHORSHIP

Conception and design of study: AHS; data acquisition: FF, AI; analysis and interpretation: FF, AI, NLH; drafting and editing of manuscript: FF, AI, NLH, AHS; recruitment and collection of CVF samples: NLH, AHS.

CONFLICTS OF INTEREST

Prof. Shennan and Dr. Hezelgrave received financial assistance providing educational talks on preterm birth from Hologic, USA. Prof. Shennan is a member of the European and Australian perinatal advisory board facilitated by Hologic USA, and a co-investigator of a trial evaluating the use of fetal fibronectin testing for prediction of preterm birth (funding: Wellbeing of Women, fetal fibronectin test kits provided by Hologic, USA).

The other authors report no conflict of interest.

Part of this work in abstract form has been presented at the British Maternal and Fetal Medicine Society's 17th annual conference, London, UK, 23-24 April 2015.

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FIGURE CAPTIONS

FIGURE 1. Study design

Standards for the Reporting of Diagnostic accuracy studies (STARD) flow chart.

BFM, bulging fetal membranes; *qfFN*, quantitative fFN system; *TLi*, qualitative fFN system; *sPTB*, spontaneous preterm birth.

FIGURE 2. Time to delivery as a function of fFN levels

Correlation between increasing values of fFN concentration and number of days elapsed from testing to delivery (n=62).

FIGURE 3. ROC curves: diagnostic performance of the two fFN tests

ROC curves for the prediction of sPTB within 14 days from testing (A) and before 34 weeks of gestation (B), for both the quantitative 10Q system (blue) and the qualitative TLi_{IQ} system (green). The midline diagonal segment (red) represents the random classifier (area=0.5).

Table 1. Demographic & clinical characteristics (n=62).

Characteristic	Value
Age (*years*)	32 ± 6
BMI (kg/m^2)	28 ± 5
Ethnicity	
White	21 (34%)
Black	36 (58%)
Other	5 (8%)
Symptoms of bulging membranes	9 (15%)
Previous sPTB	19 (31%)
Previous premature pre-labour rupture of membranes	10 (16%)
Previous second-trimester miscarriage	26 (42%)
Previous cervical surgery	10 (16%)
Smoking	
Current	4 (6%)
Ex-smoker	9 (15%)
Never	45 (73%)
History of domestic violence	4 (6%)
History of recreational drug use	4 (6%)
Median gestational age at testing	24^{+0} (21^{+2}-25^{+3})
Median gestational age at delivery	34^{+4} (25^{+2}-39^{+0})

Data reported as mean ± SD, n (%), or median (LQ-UQ). *sPTB*, spontaneous preterm birth.

Table 2. Distribution of women according to qfFN concentration and associated rates of sPTB.

Quantitative fFN category (ng/ml)	N (%)	Spontaneous preterm birth rate, n (%)			
		Within 14 days	<30 wks	<34 wks	<37 wks
<10	11 (18%)	0 (0%)	1 (9%)	2 (18%)	3 (27%)
10-49	14 (23%)	1 (7%)	1 (7%)	2 (14%)	4 (29%)
50-199	20 (32%)	4 (20%)	9 (45%)	11 (55%)	14 (70%)
200-499	8 (13%)	2 (25%)	3 (38%)	7 (88%)	7 (88%)
≥500	9 (15%)	6 (67%)	8 (89%)	8 (89%)	8 (89%)
Total	62	13 (21%)	22 (36%)	30 (48%)	36 (58%)

Table 3. Prediction of spontaneous preterm birth within 14 days from testing.

Predictive variable	Fetal fibronectin threshold			
	10 ng/ml	50 ng/ml	200 ng/ml	500 ng/ml
Sensitivity (%)	100	92	62	46
Specificity (%)	22	49	82	94
Positive Predictive Value (%)	26	32	47	67
Negative Predictive Variable (%)	100	96	89	87
Likelihood ratios				
Positive	1.29	1.81	3.35	7.54
Negative	0	0.16	0.47	0.57
Relative risk (95% CI)	1	2.8 (0.4-22.5)	3.5 (0.4-32.8)	9.3 (1.3-65.2)
Area under ROC	0.81 (95% CI 0.69-0.94)			

Table 4. Prediction of spontaneous preterm birth before 34 weeks of gestation.

Predictive variable	Fetal fibronectin threshold			
	10 ng/ml	50 ng/ml	200 ng/ml	500 ng/ml
Sensitivity (%)	93	87	50	27
Specificity (%)	28	66	94	97
Positive Predictive Value (%)	55	70	88	89
Negative Predictive Variable (%)	82	84	67	59
Likelihood ratios				
Positive	1.30	2.52	8.00	8.53
Negative	0.24	0.20	0.53	0.76
Relative risk (95% CI)	1	3.9 (1.0-14.8)	6.1 (1.7-22.7)	6.2 (1.7-22.9)
Area under ROC	0.84 (95% CI 0.73-0.95)			

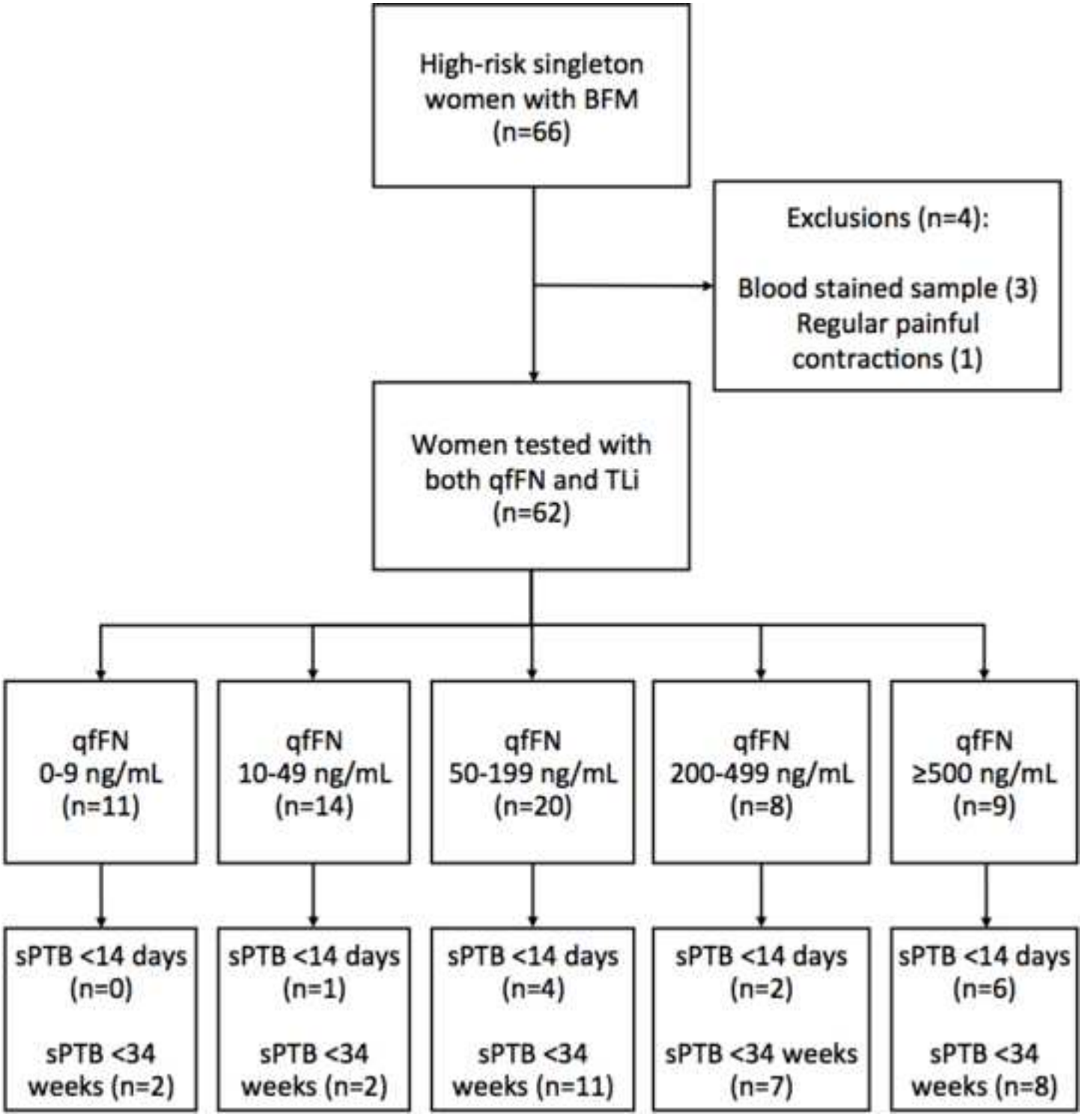


Figure 2

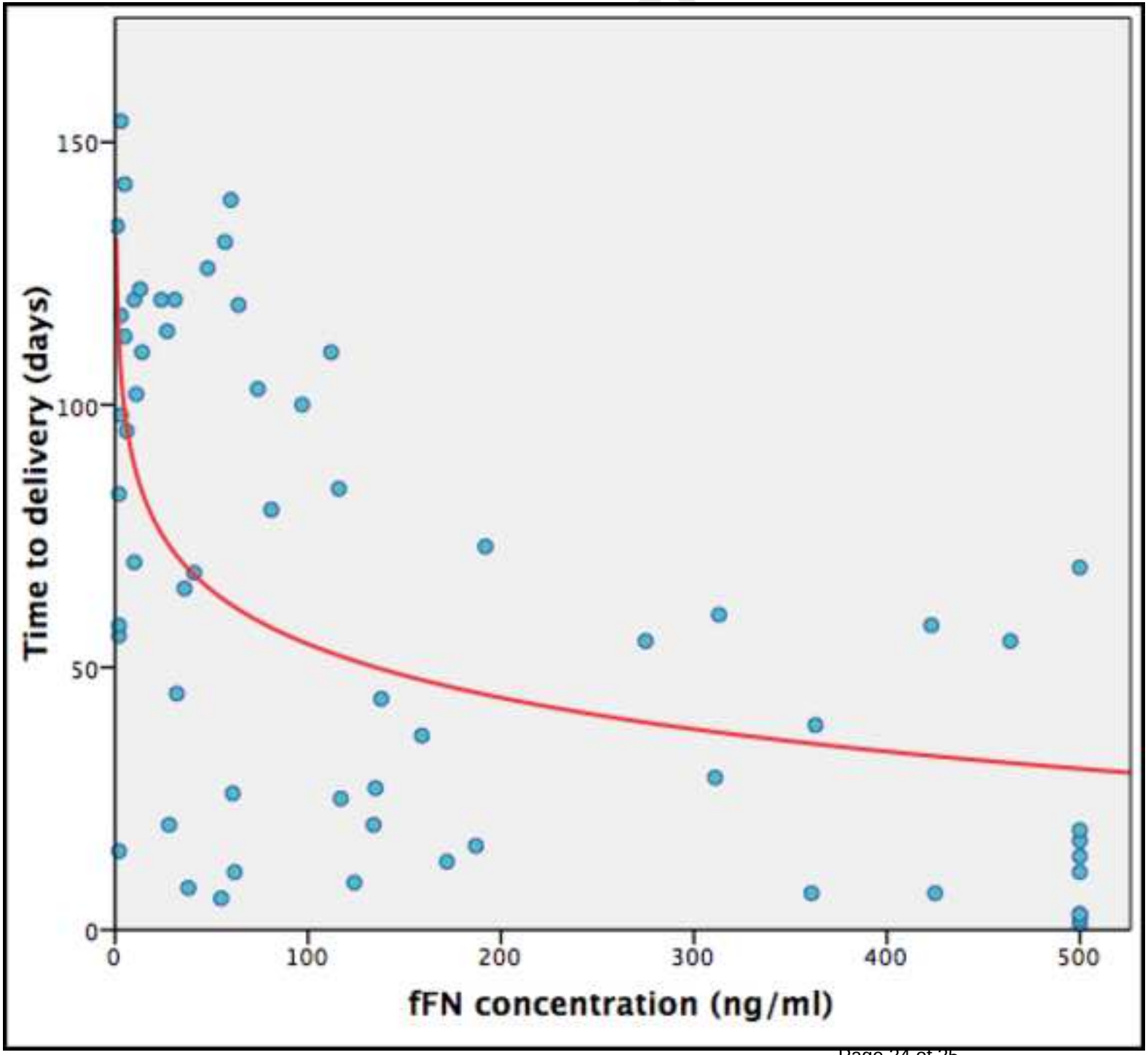
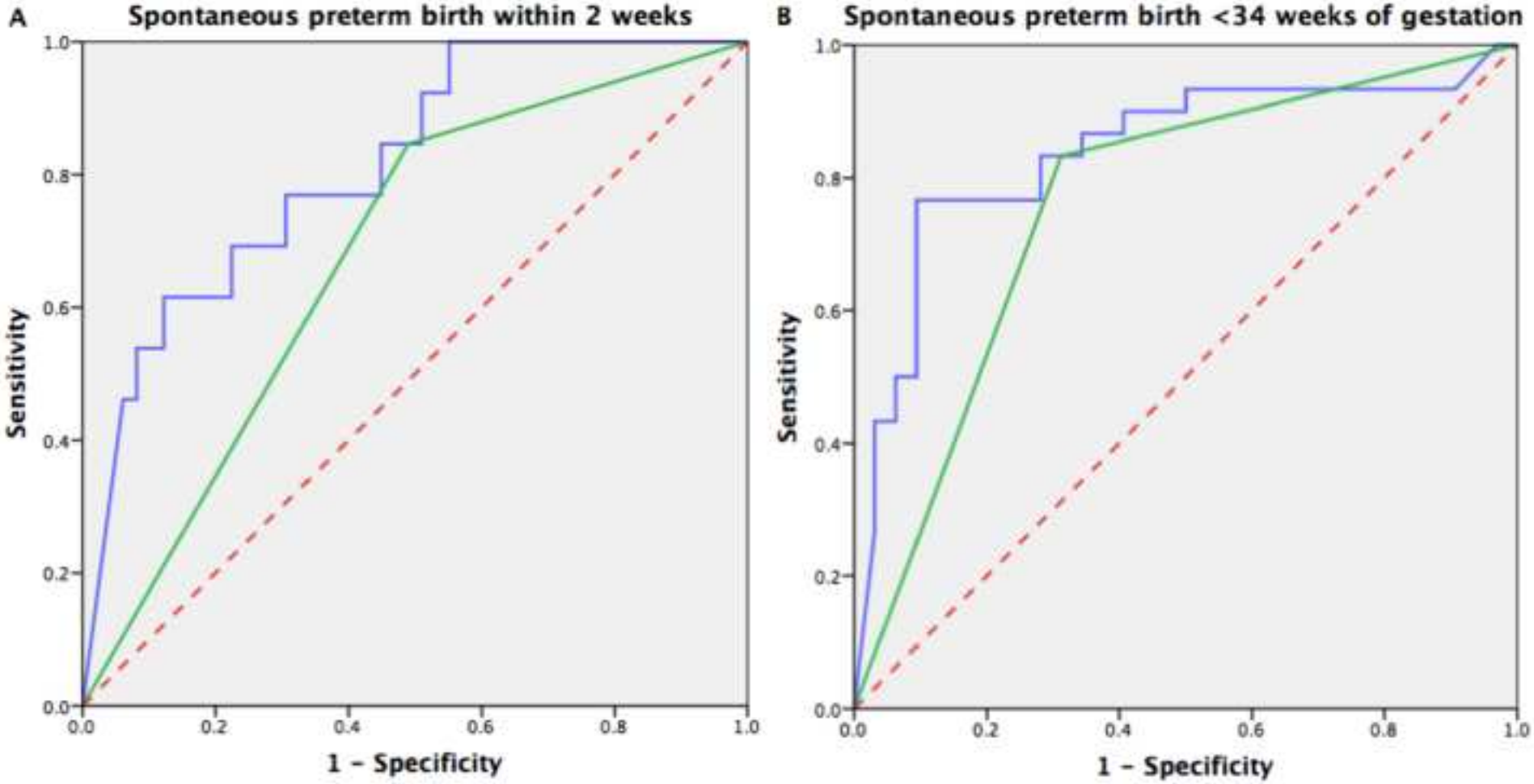

Time to delivery (days)
150
100
50
0
0
100
200
300
400
500
fFN concentration (ng/ml)

Figure 3


A
Spontaneous preterm birth within 2 weeks
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
B
Spontaneous preterm birth <34 weeks of gestation
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0